AMENDMENTS TO THE CLAIMS

Claims 1-174 (cancelled).

175. (New) A method for determining the stage of neurofibrillary degeneration associated with a tauopathy in a subject believed to suffer from the disease, which method comprises the steps of:
(i) introducing into the subject a ligand capable of labelling aggregated paired helical filament (PHF) tau protein,

wherein the ligand is capable of crossing the blood brain barrier, and

wherein the ligand is conjugated, chelated, or otherwise associated, with a detectable chemical group,
(ii) determining the presence and\or amount of ligand bound to extracellular aggregated PHF tau in the medial temporal lobe of the brain of the subject,
(iii) correlating the result of the determination made in (ii) with the extent of neurofibrillary degeneration in the subject.

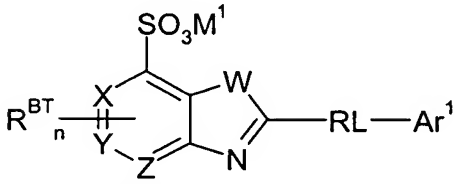
176. (New) A method as claimed in claim 175 for use in the diagnosis or prognosis of a tauopathy in a subject believed to suffer from said disease.

177. (New) A method as claimed in claim 176 wherein the tauopathy is Alzheimer Disease (AD).

178. (New) A method as claimed in claim 175 wherein the extent of neurofibrillary degeneration is related to the neuropathological staging of the progression of AD according to the defined hierarchical system shown in Figure 2c.

179. (New) A method as claimed in claim 175 wherein the ligand is labelled for SPECT and is not capable taken up intracellularly or the ligand is labelled for positron emission tomography (PET).

180. (New) A method as claimed in claim 175 wherein the ligand is a compound of the formula:



wherein:

W is S, O, or NH;

exactly one of X, Y, and Z is CH or N;

the others of X, Y, and Z are CH;

M^1 is an alkali metal cation selected from: Li, Na, K, or Cs.

RL is a rigid linker group;

Ar^1 is an C_{5-20}aryl group;

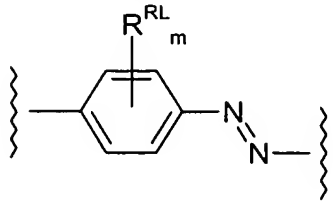
n is an integer from 0 to 3; and,

each R^{BT} is independently a core substituent selected from: C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, nitro, cyano, halo, or amino.

181. (New) A method as claimed in claim 180 wherein the twist is no greater than that of the compound of Figure 16.

182. (New) A method as claimed in claim 180 wherein n is 1, and R^{BT} is independently -Me, -Et, -nPr, or -iPr.

183. (New) A method as claimed in claim 180 wherein RL is a group of the formula:

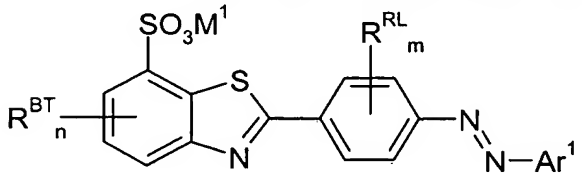


wherein:

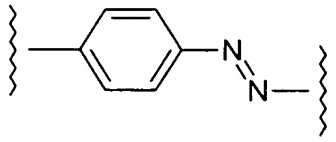
m is an integer from 0 to 4, and

each R^{RL} is independently a rigid linker aryl substituent,

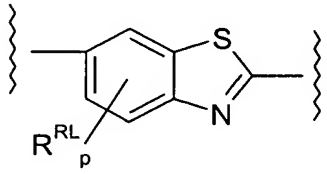
and the ligand has the formula:



184. (New) A method as claimed in claim 183 wherein RL is a group of the formula:



185. A method as claimed in claim 183 wherein RL is a group of the formula:

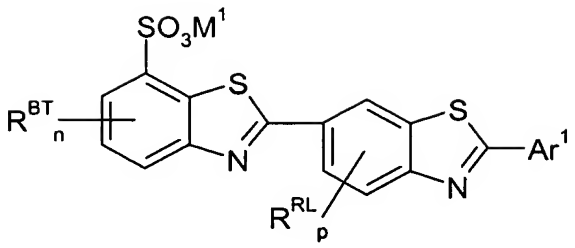


wherein

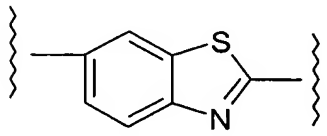
p is an integer from 0 to 3, and

each R^{RL} is independently a rigid linker aryl substituent,

and the compounds have the formula:



186. (New) A method as claimed in claim 185 wherein RL is a group of the formula:



187. (New) A method as claimed in claim 180 wherein Ar^1 is selected from:

groups derived from benzene (C_6), naphthalene (C_{10}), anthracene (C_{14}), phenanthrene (C_{14}), naphthacene (C_{18}), and pyrene (C_{16}), and

C_5heteroaryl groups derived from furan (oxole), thiophene (thiole), pyrrole (azole), imidazole (1,3-diazole), pyrazole (1,2-diazole), triazole, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, and oxatriazole; and

C_6heteroaryl groups derived from isoxazine, pyridine (azine), pyridazine (1,2-diazine), pyrimidine (1,3-diazine), pyrazine (1,4-diazine), triazine, tetrazole, and oxadiazole (furazan), and

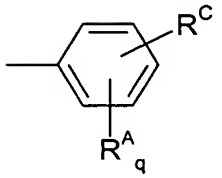
C_9heterocyclic groups derived from benzofuran, isobenzofuran, indole, isoindole, purine, benzimidazole;

C_{10}heterocyclic groups derived from quinoline, isoquinoline, benzodiazine, pyridopyridine, quinoxaline;

C_{13}heterocyclic groups derived from carbazole; and,

C_{14}heterocyclic groups derived from acridine, xanthene, phenoxathiin, phenazine, phenoxazine, phenothiazine.

188. (New) A method as claimed in claim 187 wherein Ar^1 is an aryl group having a phenyl core, and has the formula:



wherein

q is an integer from 0 to 5; and

each R^A is independently an aryl substituent;

wherein each R^A is independently selected from:

-OH, $-NH_2$, $-NHR^1$, $-NR^1R^2$, $-SO_3M^2$, and C_{1-4}alkyl;

wherein:

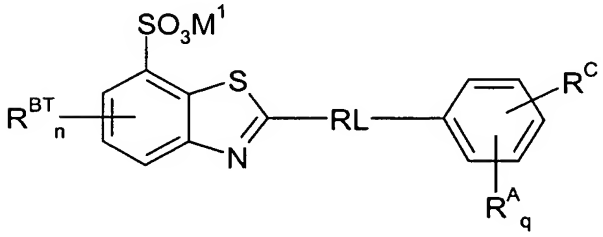
R^1 and R^2 are each C_{1-4}alkyl, and

M^2 is an alkali metal cation selected from Li, Na, K, or Cs

R^C, if present, is a reactive conjugating substituent, or

R^C is, or contains, a detectable label;

and the compound has the formula:



189. (new) A method as claimed in claim 188 wherein R^C is present and is a reactive conjugating substituent, and is, or contains,

a reactive functional group suitable for conjugation to another molecule by chemical reaction therewith, to form a covalent linkage therebetween, or

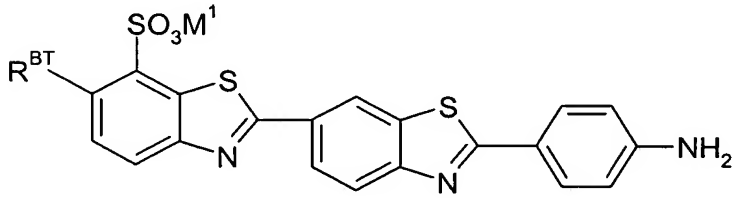
a moiety suitable for conjugation to another molecule by a strong non-covalent interaction, or

a moiety suitable for conjugation to another molecule by complex or chelate formation.

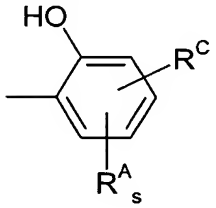
190. (New) A method as claimed in claim 189 wherein R^C is present and is, or contains, a technetium-chelating group.

191. (New) A method as claimed in claim 188 wherein R^C is present and is, or contains, a detectable label selected from: a dye, a fluorescent marker, an antigenic group, a stable or an unstable isotope, or a positron-emitting carbon atom.

192. (New) A method as claimed in claim 186 wherein the ligand has the formula:



193. (New) A method as claimed in claim 188 wherein Ar^1 is an aryl group having a hydroxy-substituted phenyl core, and has the formula:



wherein

s is an integer from 0 to 4, and

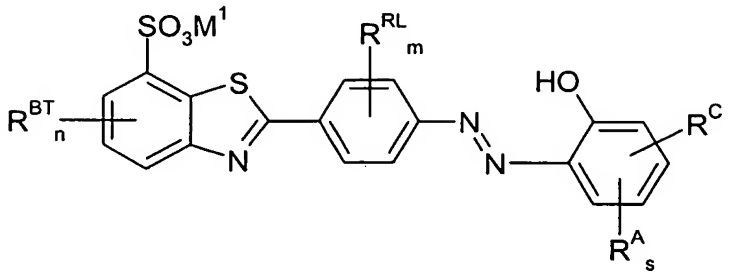
each R^A is independently an aryl substituent, and

R^C, if present, is a reactive conjugating

substituent, or

R^C is, or contains, a detectable label.

194. (New) A method as claimed in claim 193



wherein:

M^1 is an alkali metal cation selected from Li, Na, K, or Cs;

n is an integer from 0 to 3;

each R^{BT} is a independently benzothiazole substituent;

m is an integer from 0 to 4;

each R^{RL} is independently a rigid linker aryl substituent;

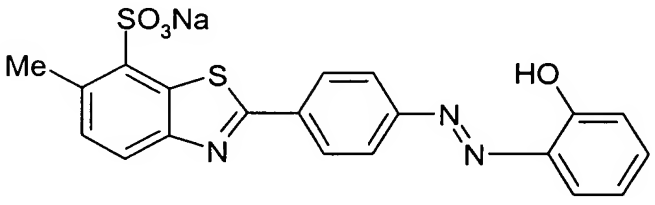
s is an integer from 0 to 4;

each R^A is independently an aryl substituent; and,

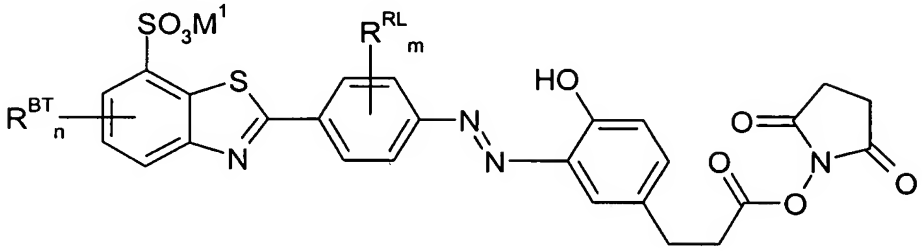
R^C, if present, is a reactive conjugating substituent, or

R^C is, or contains, a detectable label.

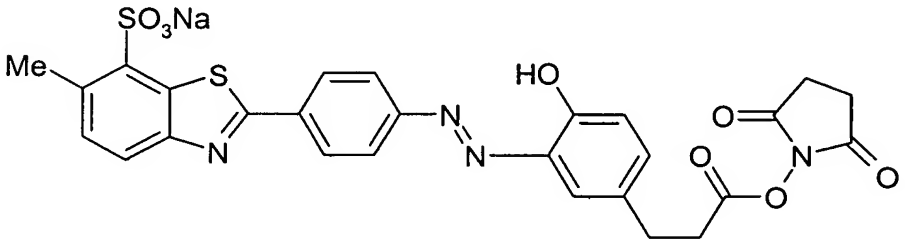
195. (New) A method as claimed in claim 194 wherein the ligand has the formula:



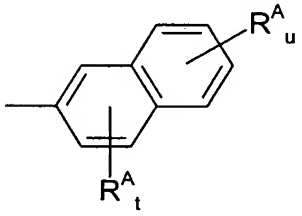
196. (New) A method as claimed in claim 195 wherein the ligand has the formula:



197. (New) A method as claimed in claim 196 wherein the ligand has the formula:



198. (New) A method as claimed in claim 197 wherein Ar^1 is an aryl group having a naphthyl core, and has the formula:



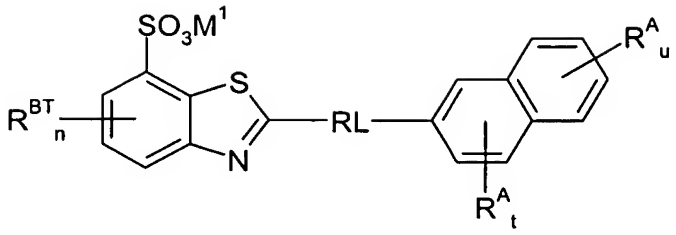
wherein

t is an integer from 0 to 3,

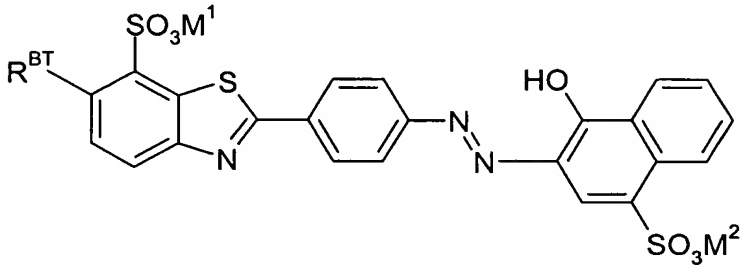
u is an integer from 0 to 4, and

each R^A is independently an aryl substituent,

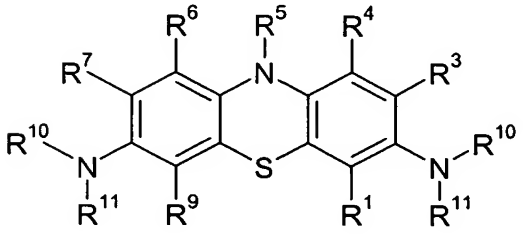
and the compound has the formula:



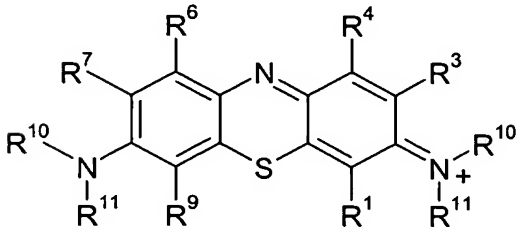
199. (New) A method as claimed in claim 198 wherein the ligand has the formula:



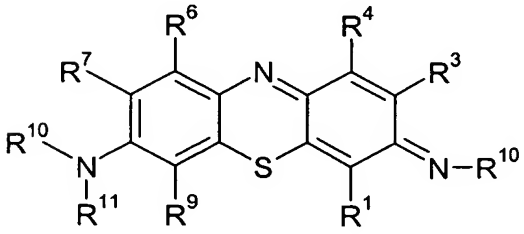
200. (New) A method as claimed in claim 175 wherein the ligand is a compound of one of the following formulae:



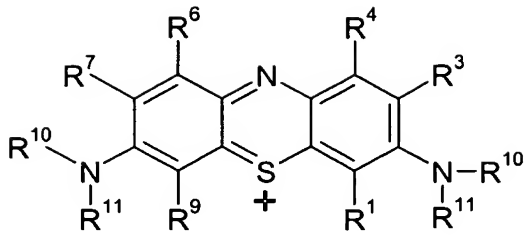
(I)



(II)



(III)



(IV)

wherein:

each of R_1, R_3, R_4, R_6, R_7 and R_9 is independently hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted alkyl, haloalkyl, or alkoxy;

R_5 is independently hydrogen, hydroxy, carboxy, substituted or unsubstituted alkyl, haloalkyl, or alkoxy;

R_{10} and R_{11} are independently selected from hydrogen, hydroxy, carboxy, substituted or unsubstituted alkyl, haloalkyl, or alkoxy;

or a pharmaceutically acceptable salt thereof.

201. (New) A method as claimed in claim 200 wherein the ligand is an acid addition salt formed between a compound described in said claims and an acid which is an inorganic acid or an organic acid.

202. (New) A method as claimed in claim 201 wherein the ligand is shown in Figure 8b.

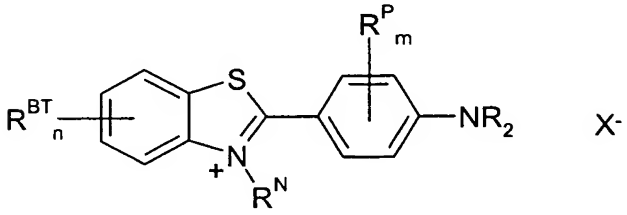
203. (New) A method as claimed in claim 200 wherein the ligand comprises a positron-emitting carbon.

204. (New) A method as claimed in claim 175 which further comprises the step of additionally determining the presence and\or amount of a ligand bound to intracellular aggregated tau in a neocortical structure of the brain of the subject.

205. (New) A method as claimed in claim 204 wherein the ligand used to bind to extracellular aggregated PHF tau in the medial temporal lobe and the ligand used to bind to intracellular aggregated PHF tau in the neocortical structure of the brain are labelled distinctively.

206. (New) A method as claimed in claim 175 wherein steps (i) and\or (ii) of the method are performed in conjunction with the further step of introducing into the subject a further blocking ligand which labels the competing binding sites present in the relevant region of the brain preferentially to the ligand used to bind aggregated PHF tau.

207. (New) A method as claimed in claim 206 wherein the blocking ligand is selected from the list consisting of:
[^{18}F] FDDNP;
a benzthiazole of the formula:



wherein:

n is an integer from 0 to 4;

each R^{BT} is independently a blocking ligand benzothiazole substituent which is independently C_{1-4}alkyl, -SO_3H, or -SO_3M^3, wherein M^3 is a cation,

m is an integer from 0 to 4;

each R^P is independently a phenylene substituent;

each R is independently -H or an amino substituent; and,

either:

R^N and X^- are both absent and the associated

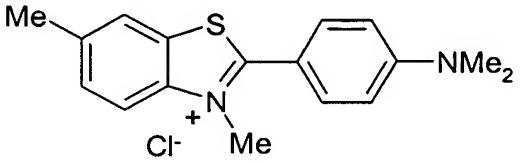
(tertiary) nitrogen atom is neutral;

or:

R^N is a benzothiazolino substituent and the associated (quaternary) nitrogen atom bears a positive charge, and X^- is a counter ion.

208. (New) A method as claimed in claim 207 wherein the blocking ligand is thioflavin-T.

209. (New) A method as claimed in claim 207 wherein the blocking ligand is a benzthiazole of the formula:



210. (New) A method as claimed in claim 207 wherein the blocking ligand is a benzthiazole of the formula: